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# **Developmental origins of suicide: systematic review and meta-analysis of the in utero and perinatal influences on suicide risk**

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## Summary

**Background.** Adverse in-utero and perinatal conditions may contribute to a heightened suicide risk throughout the lifespan, however existing evidence is sparse and contradictory. We did a systematic review and meta-analysis to investigate in-utero and perinatal exposures associated with suicide, suicide attempt, and suicidal ideation.

**Methods.** We searched MEDLINE, Embase, and PsycINFO from inception to January 24, 2019 for population-based prospective studies investigating the association between in-utero and perinatal factors and suicide, suicide attempt, and suicidal ideation. We calculated pooled odds ratio (ORs) with 95% CIs using random-effects models and used meta-regression to investigate heterogeneity.

**Findings.** We identified 42 studies; they had a low risk of bias (median quality score 9/9; range 5-9). Family/parental characteristics, such as high birth order (eg, pooled ORs fourth or later born vs first born 1.52, 1.21-1.88), teenage mothers (1.80, 1.52-2.14), single mothers (1.57, 1.31-1.89), indices of socioeconomic position such as low maternal (1.36, 1.28-1.46) and paternal (1.38, 1.27-1.51) education, and foetal growth - low birthweight (1.30, 1.09-1.55) and small-for-gestational-age (1.18, 1.00-1.40) were associated with higher suicide risk. Father's age, low gestational age, obstetric characteristics (eg, caesarean section), and condition/exposure during pregnancy (eg, maternal smoking or hypertensive disease) were not associated with higher suicide risk. Similar patterns of associations were observed for suicide attempt and suicidal ideation; however, these results were based on a lower number of studies. In meta-regression, differences in length of follow-up explained most between-study heterogeneity.

**Interpretation.** These findings suggest that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, supporting the developmental origin of health and diseases hypothesis for suicide. The low number of studies for some risk factors, especially for suicide attempt and ideation, leaves gaps in knowledge that need to be addressed. The mechanisms underlying the reported associations, and their causal nature still remain unclear.

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## **Introduction**

Suicide is an important cause of mortality worldwide, with an estimated global burden of 800 000 deaths each year,<sup>1</sup> and its prevention is of paramount importance. The need for prevention extends to non-fatal suicide attempt and severe suicidal ideation, as both carry serious long-term consequences<sup>2</sup> including increased risk of suicide death.<sup>3</sup>

Suicide is a complex and multifactorial phenomenon with both proximal (eg, mental disorders, economic breakdowns) and distal (eg, childhood adversities) risk factors.<sup>4</sup> In keeping with the developmental origins of health and disease (DOHaD) model,<sup>4-8</sup> an increasing number of studies have reported associations of in-utero and perinatal factors with suicide and mental disorders.<sup>9,10</sup> While the contribution of in-utero and perinatal conditions is well established for a range of non-communicable diseases such as cardiovascular and metabolic comorbidities,<sup>11-13</sup> evidence is less consistent for psychiatric disorders and suicide.<sup>14,15</sup> For example, prior studies have reported an increased risk of suicide for individuals born with a low birthweight<sup>16</sup> or individuals exposed to maternal smoking during pregnancy,<sup>17</sup> whereas others have failed to replicate these associations.<sup>18,19</sup> Such inconsistencies may be accounted for by heterogeneity of studies in terms of country of origin, study design and length of follow-up. Further, as both suicide and most in-utero/perinatal factors (such as low birthweight) are rare at the population-level, failure to find an association in some studies may be attributable to the lack of statistical power despite large sample sizes. We are unaware of any systematic review of the in-utero and perinatal influences on suicide using statistical approaches increasing the statistical power (such as meta-analysis).

We conducted a systematic review and meta-analysis of the available evidence on the association between in-utero and perinatal risk factors (including in-utero conditions, maternal-related factors, and socioeconomic conditions at birth) and suicide, suicide attempt, and suicidal ideation. Findings from such a study may provide insight supporting the DOHaD hypothesis for suicide risk, thus informing public health preventive interventions focusing on early maternal and child care.

## **Methods**

### **Search strategy and selection criteria**

This systematic review was conducted in accordance with Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.<sup>20</sup> The protocol was registered in PROSPERO (number CRD42018091205). A health science librarian (JB) searched the following databases from their inception until January 24, 2019 for published studies on in-utero and perinatal factors and suicide: MEDLINE, Embase, and PsycINFO. The search was restricted to studies

published in English. Additionally, we searched the reference lists of all identified publications and hand searched key journals. Only published studies were considered. A search strategy was developed for MEDLINE and modified for the other databases. Using a combination of free text and controlled vocabulary terms (see **appendix**), we searched terms from three categories: in-utero and perinatal factors (eg, “birthweight”, “parent\* age”, “foetal growth”), suicide-related outcomes (eg, “suicide\*”, “suicide attempt”, “suicidal ideation”, “self-harm”), and studies with a prospective design (eg, “longitudinal”, “registries”, “epidemiological studies”), combined using the Boolean operator “and”.

Two investigators (MO and DB) independently screened the identified records for eligibility, first by title or abstract, followed by assessing the full-text (agreement on inclusion, weighted  $k = 0.98$ ); discrepancies were resolved by discussion with a third investigator (MCG). Studies were included if they: (1) were population-based longitudinal studies or case-control studies nested in a cohort (ie, linkage of population registries or population-based cohort studies), and (2) reported on associations between any in-utero (any gestational period) and perinatal (measure up to one year of age) exposures or conditions and suicide, suicide attempt or suicidal ideation. Studies assessing self-harm defined as non-suicidal self-injuries were excluded.

### **Data extraction and quality assessment**

Two investigators (MO and DB) independently extracted the following information from the selected articles: name of the first author, year of publication, name of the cohort (or information about the register), study location (country), number of participants, birth year of the participants, year at which the outcomes were assessed, participants’ age at outcome assessment, risk factors investigated, outcome(s) investigated, number of cases and non-cases among exposed and non-exposed to each risk factor. If information was unavailable or unclear from a published report, corresponding authors were contacted to obtain the relevant data.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.<sup>21</sup> The scale assesses the quality of three domains of a study: participant selection (eg, representativeness of the exposed cohort), comparability of exposed and non-exposed groups (eg, whether the analysis accounted for confounding factors), and ascertainment of outcome (eg, adequacy of follow-up). For each characteristic within these three domains, a point was given if the criterion was fulfilled, except for comparability criterion that could score 0, 1 or 2 points (score range, 0-9). Two investigators (MO and DB) independently assessed the quality of the articles. Agreement between the investigators was high (weighted  $k = 0.86$ ), and remaining discrepancies were resolved by discussion with a third investigator (MCG).

### **Data analysis**

We did separate meta-analyses to estimate the association between each identified risk factor and suicide, suicide attempt, and suicidal ideation when raw data were provided for at least 2 studies. When it was not possible to pool the estimates, or information to perform meta-analysis was lacking (ie, single studies), we summarized evidence narratively. Our procedure to harmonize exposure categorization across studies is described in **appendix**. For exposures investigated in more than one study from the same cohort/linkage, we selected the study with the longest follow-up. We calculated crude odds ratios (OR) and 95% confidence intervals (CIs) to compare lifetime suicide risk of individuals exposed to a given risk factor versus those non-exposed. Pooled ORs with 95% CIs were calculated using random-effect models.<sup>22</sup> Given the range of different measures used to compute adjusted associations (eg, hazard ratios, odds ratios), adjustment variables investigated (eg, socioeconomic position, mental health), and exposure categorisation (eg, mother's age <20 versus  $\geq 20$  in one study, and <20 versus 20-25 versus  $\geq 25$  in another), we were not able to pool consistent adjusted estimates. However, we narratively reported whether adjusting for confounding variables yielded changes in the crude estimates in the single studies and performed sensitivity analyses. Forest plots were generated showing ORs with corresponding 95% CIs for each study and the overall random-effect pooled estimate. We assessed heterogeneity across studies using the Cochrane Q statistic and the  $I^2$  statistic (higher values representing higher heterogeneity),<sup>23</sup> and used meta-regression and subgroup analyses to explore potential sources of heterogeneity (ie, age at follow-up, study design, and differences in the categorization of the exposure variables) and the influence of individual studies. Risk of publication bias was assessed with visual inspection of the funnel plots, and further inspected using the Egger test<sup>24</sup> and the Duval and Tweedie trim-and-fill method.<sup>25</sup>

### **Role of funding sources**

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## **Results**

From the initially retrieved 3013 unique records, 42 articles met our inclusion criteria (**Figure 1**) and were retained for this study. The articles consisted of data that were drawn from 21 different cohorts (n=10 cohort studies and n=11 population registers) from Europe (n=15), North America (n=3), Taiwan (n=1), and New Zealand (n=1), and Brazil (n=1). Sample sizes ranged from 140 to 3 300 708, and follow-up from 2 to 70 years. Suicide mortality was an

outcome in 14 of 21 cohorts, suicide attempt in 9 of 21, and suicidal ideation in 4 of 21 (**Table 1**). Methodological quality of the retained studies was high for observational studies (overall satisfactory quality of evidence; **Table 2**): most studies showed limited evidence of selection bias, had long follow-up and were based on secure records for the assessment of exposures and outcomes (eg, linkage of hospital or death registers).

**Figure 2** shows the perinatal factors investigated in the included studies. Studies investigating the association between family and parental characteristics and suicide risk suggested that suicide risk was heightened for second or later born individuals compared to first born individuals. The pooled OR for this comparison was 1.22 (95%CI 1.12-1.34; n=10 studies; **Figure 3**). Restricting the analysis to 7 of the 10 studies allowed us to test dose-response associations between birth order and suicide: the pooled OR for the comparison between second-to-third born versus first born was 1.18 (1.07-1.30) and for the comparison between fourth or later born and first born was 1.51 (1.21-1.88), suggesting an increased suicide risk for increasing birth order. Most studies adjusting for confounding factors in multivariate analyses (such as maternal age, socioeconomic status, and sex), reported dose-response associations between increasing birth order and suicide, with adjusted associations being 10-20% stronger than crude associations. There was also evidence of an association in two within-family studies comparing siblings from the same family (thus accounting for family-related confounding factors).<sup>26,27</sup> One study showed that suicide risk was similar when the analyses were stratified according to the time since the birth of the previous child (eg, adjusted hazard ratio [HR] were 1.41 when the previous child was born 2 years earlier, 1.24 when the child was born 2-3 years earlier, and 1.49 when the child was born >3 years earlier),<sup>26</sup> while another study showed that suicide risk persisted when the analyses were stratified by sibship size.<sup>28</sup> The association, however, was less clear for suicide attempt. The risk of suicide attempt was not heightened for second or later born children compared to first born children, with a pooled OR of 1.17 (0.97-1.41, n=5 studies; **Figure 4**). One study only found statistical evidence for an association between birth order and suicidal ideation for the comparison between fourth or later born children versus first born children (adjusted OR 1.48, 1.06-2.07).<sup>29</sup> For mother's age at child birth, suicide risk was heightened for offspring of younger mothers (<20 years of age) compared to those born to older mothers ( $\geq$ 20 years of age), with a pooled OR of 1.80 (1.52-2.14, n=7 studies). Adjustment for various confounding factors in single studies (eg, birth order, socioeconomic status) did not account for this association. Associations were also found for suicide attempt and younger mothers (pooled OR 1.81, 1.32-2.50, n=4 studies) but not for suicidal ideation (pooled OR 1.28, 0.84-1.94, n=2 studies). No evidence of increasing suicide risk was found for individuals born to young (<25 years) or older fathers (>35 years) compared to those born to fathers aged 25-35, with pooled ORs of 1.24 (0.90-1.71, n=4 studies) and 1.05 (0.88-1.25, n=4 studies),

respectively. However, subgroup analyses stratified by age at outcome assessment indicated that indicated that in studies with >30 years follow-up there was evidence of increased risk amongst those with older fathers. Additionally, one study using a robust within-sibling design reported heightened risk of suicide attempt for offspring born to fathers aged 45 years or older compared to fathers aged 20-24 years (HR 2.72, 2.08-3.56).<sup>30</sup> For household composition at child birth, the pooled OR for the comparison between single-mother households (ie, single, widowed, divorced mothers at child birth) versus non-single mother households was 1.57 (1.31-1.89, n=7 studies). Most studies adjusted for relevant confounding factors, such as socio-economic status, child sex, and other family variables (eg, maternal age), and no major variations in the estimates was detected. These results were consistent for suicide attempt (pooled OR 1.78, 1.29-2.45, n=3 studies), but no association was reported for suicidal ideation in one study (OR 1.21, 0.86-1.37).<sup>31</sup>

For variables describing family socioeconomic position at birth, the pooled OR for higher versus lower parental education (ie, up to primary/lower secondary school) was similar for mothers (1.36, 1.28-1.46, n=3 studies) and fathers (1.38, 1.27-1.51, n=2 studies). Adjustment for confounding factors (eg, parental age, birthweight and birth order) did not explain associations in any of the studies. Suicide attempt (OR 1.33, 0.96-1.83)<sup>32</sup> and suicidal ideation (OR 0.94, 0.82-1.14)<sup>31</sup> were not associated with maternal education in the two studies that investigated this, although for suicide attempt the strength of the association (OR 1.33) was consistent with that seen for suicide. Individuals from low socioeconomic status at birth (parents' unskilled/manual work) were at increased risk of suicide (pooled OR 1.27, 1.00-1.61, n=6 studies) or suicide attempt (pooled OR 1.75, 1.45-2.09, n=5 studies) but not suicidal ideation (OR 1.23, 0.76-1.57),<sup>31</sup> compared to individuals with higher socioeconomic status.

Several studies investigated the association between various indices of foetal growth and suicide risk. Evidence of increased risk was found across five studies comparing suicide risk for individuals with low (<2500 g) versus normal birthweight ( $\geq$ 2500 g), with a pooled OR of 1.30 (1.09-1.55). Such risk was not explained by other in-utero and maternal confounding variables (eg, gestational age, obstetric characteristics, mother's age and parity). Consistently, there was an increased risk of suicide attempt (pooled OR 1.39, 1.23-1.56, n=2 studies) and suicidal ideation (pooled OR 1.73, 1.04-2.86, n=2 studies) for individuals born with low birthweight. Low gestational age at birth (ie, prematurity) was not associated with suicide, with a pooled OR of 1.11 (0.98-1.25; n=5 studies) for low (<36/38 weeks) versus non-low gestational age ( $\geq$ 36/38 weeks). However, an association was found for being small for gestational age at birth, with a pooled OR of 1.18 (1.00-1.40, n=4 studies). Concerning suicide attempt, an association was reported for low gestational age in two studies (pooled OR 1.09, 1.04-1.15), although this comparison



was mainly influence by one study (99.8% weights). One study reported a higher risk in the lowest category of birth length (<47 cm) relative to the reference category (50–51 cm), with a crude HR of 1.36 (1.01-1.84) for suicide and an adjusted HR of 1.29 (1.18-1.41) for suicide attempt.<sup>16</sup> One study reported no association between small head circumference at birth (<32 cm versus  $\geq$ 32 cm) and suicide,<sup>17</sup> but another study reported an association with suicide attempt (adjusted OR 2.2, 1.1-4.6).<sup>33</sup>

Several studies investigated associations between obstetric characteristics and suicide but found no statistical evidence of an association with caesarean section versus vaginal delivery (pooled OR 1.13, 0.92-1.40, n=2 studies) and placenta abruption (adjusted HR 1.60, 0.51-4.98).<sup>17</sup> Similarly, a study found no statistical evidence of an association between 5-min Apgar score <7 and suicidal ideation (adjusted OR 1.9, 0.73-5.0),<sup>33</sup> whereas another study reported an association between caesarean section and suicide attempt (OR 1.09, 1.00-1.18).<sup>16</sup>

Finally, maternal physical and psychological prenatal conditions and exposures during pregnancy were investigated for their association with suicide risk. Four studies investigated associations between maternal smoking during pregnancy and suicide mortality. The pooled OR for the comparison between mothers smoking  $\geq$ 1 cigarettes/day versus mothers smoking <1 cigarettes/day was 1.56 (0.99-2.46, n=4 studies). Studies investigating the number of cigarettes/day did not report a clear dose response association.<sup>17,34</sup> It is worth noting that these studies revealed potential confounding effects of perinatal and family variables: in one study, the effect of maternal smoking was only seen for the comparison between mother smoking >10 vs <1 cigarettes/day after adjustment for child's sex, gestational age, birthweight, 5-minute Apgar score, maternal age, parity, and mother's psychiatric diagnosis before the child's birth.<sup>34</sup> In another study, the effect of maternal smoking was attenuated when the analysis was restricted to sibling pairs discordant for suicidal acts and prenatal smoking exposure.<sup>17</sup> Weak evidence for an association with suicide was reported for mother chronic illness<sup>35</sup> and exposure to diethylstilboestrol during pregnancy,<sup>36</sup> and for both suicide and suicide attempt for bereavement stress during preconception (ie, death of a first-degree relative),<sup>37</sup> mother hypertensive disease (pooled OR suicide 1.09, 0.69-1.72, n=2 studies; HR suicide attempt 1.27, 1.00-1.63),<sup>16</sup> mother's antenatal depressive mood,<sup>38</sup> and unwanted pregnancy.<sup>38</sup> It is worth noting, however, that these comparisons were based on relatively few events.

We found high heterogeneity for most pooled estimates. Meta-regression suggested that 36 to 100% of this heterogeneity could be explained by the age at follow-up ( $\leq$ 30 years versus >30 years), but accounting for this factor would not alter our results (**appendix**). No heterogeneity was explained by study design, and differences in the

categorization of the exposure variables. When single studies explaining the remaining heterogeneity were removed, the pooled estimate did not change (**appendix**).

Subgroup analyses, although based on a small number of studies, suggested that associations of maternal age and single motherhood were more pronounced among studies with shorter follow-up ( $\leq 30$  years), whereas associations for birth order, paternal age and parental education were more pronounced among studies with longer follow-up ( $> 30$  years) (**Figure 5**). For all comparisons, we found little evidence that publication bias could have influenced our results (**appendix**). Sensitivity analyses suggested that confounding factors are unlikely to explain the reported associations.

## Discussion

To our knowledge, this is the first systematic review and meta-analysis summarizing the available evidence of the in-utero and perinatal influences on suicide. We showed that in-utero and perinatal influences, especially family/parental characteristics, socioeconomic characteristics, and indices of foetal growth, are associated with increased suicide risk several decades later. Although such findings are consistent with DOHaD hypothesis,<sup>4,10</sup> in-utero and perinatal factors are generally absent from most of the current models of suicide. Integrating the contribution of these early-life factors would improve our understanding of the aetiology of suicide and inform population-based suicide prevention efforts. However, some important issues remain to be clarified in future research.

First, many risk factors such as obstetric characteristics and conditions/exposures during pregnancy remain under-investigated. Although single studies were of high quality, additional evidence is needed to draw firm conclusions about their role on the aetiology of suicide. Moreover, no data was available for several other potentially relevant factors, such as maternal psychopathology, substance use, infections, and birth complications, that were shown to contribute to the aetiology of other mental disorders.<sup>14</sup>

Second, suicide attempt and suicidal ideation were under-investigated outcomes. It is important for future studies to test whether early-life factors associated with suicide are similarly associated with non-fatal suicide attempt. Our meta-analysis suggests that while some associations are similar for suicide and suicide attempt (eg, mother's young age), for other factors (eg, birth order) the available evidence does not allow us to draw firm conclusions. Additionally, as the literature showed that many childhood/adolescence risk factors for suicidal thoughts differ from those for suicidal acts,<sup>39</sup> future studies should clarify whether this applies to in-utero and perinatal influences as well.

Given the low number of studies investigating suicidal ideation as an outcome, additional evidence on this point is needed.

Third, future studies are needed to establish the causality of associations. Although most studies adjusted for relevant confounding factors, causation cannot be established as unmeasured factors may account for observed associations.<sup>40</sup> For example, associations of adverse maternal conditions with suicide risk could be due to parental psychiatric disorders influencing both adverse maternal conditions (eg, teenage pregnancy, single motherhood) and mental health disorders in the offspring. Among the 42 included studies, only 8 investigated the confounding role of parental psychopathology (**appendix**). Although it is difficult to reach firm conclusions, we observed that associations between early-life factors and suicide outcomes persisted after adjustment for parental mental disorders, including in sibling designs. This is in line with findings from a recent study that indicates that parental psychopathology is unlikely to fully explain the association between early-life influences and mental disorders.<sup>41</sup> Additionally, although experimental studies are unfeasible or unethical, quasi-experimental approaches, based on instrumental variables or twin/sibling designs, are available.<sup>40,42</sup> Few such studies were identified in this review, and provided evidence suggesting that the association of birth order and maternal age on suicide was causal.<sup>26,27</sup> However, one study reported that the association between low birthweight and suicide attempt was fully attenuated using a sibling design.<sup>43</sup> These quasi-experimental studies account for factors that sibling share within the family, including parental psychopathology. Future studies should use such designs to prompt causal conclusions.

Fourth, suicide rather than being a single condition, is a behaviour resulting from a combination of vulnerability factors and immediate precipitant factors. Therefore, the observed associations are likely to reflect both the influence of early risk factors on mental disorder strongly associated with suicide (eg, schizophrenia, major depression), and the influence of early risk factors on behaviours, such as impulsive-aggression, that are specifically associated with suicide.<sup>44</sup> Therefore, future studies are needed to clarify whether the in-utero and perinatal risk factors for suicide identified in our meta-analysis are also related to adolescence/adult psychiatric disorders comorbid with suicide, or whether they are specific to suicide. The association between family and maternal characteristics at child birth and suicide risk is consistent with studies that found: (i) a negative dose-response association of higher birth order with adult psychiatric admissions<sup>45</sup> and mental illness,<sup>29</sup> (ii) associations of young mother's age and single mother household with behavioural and mental health problems,<sup>46,47</sup> and (iii) the association between socioeconomic adversity in childhood and adverse social, health, and mortality outcomes.<sup>48</sup> However, the absence of association between advanced father's age and suicide risk differs from the documented association between young paternal age

with behaviour syndromes and psychosis and advanced paternal age with pervasive developmental disorders/autism spectrum disorder.<sup>49</sup> On the other hand, one study suggested an increased risk of suicide attempt for individuals born from a father aged >45 years,<sup>30</sup> which calls for further investigations to ascertain whether advanced paternal age is specifically linked with non-fatal suicidal behaviours. Similarly, our meta-analysis also provides evidence for an association between low birthweight and risk for suicide, suicide attempt, and suicidal ideation that is consistent with what has been reported for ADHD, autism,<sup>43</sup> and schizophrenia,<sup>14</sup> but inconsistent with a meta-analysis that failed to report an association with depression.<sup>50</sup>

Finally, the mechanisms underlying associations between in-utero/perinatal factors and suicide should be clarified. Hypothesised mechanisms are conceptually represented in **Figure 6**. First, factors such as young mother's age, teenage mothers, single motherhood, and low socioeconomic position at birth may reflect an adverse psychosocial environment which increased level of stress in pregnant mothers.<sup>9</sup> Maternal stress may affect foetal brain development through epigenetic mechanisms (eg, alterations in the glucocorticoid receptor and the central corticotrophin hormone) or gene-by-environment interactions mechanisms (eg, via Oxytocin pathways)<sup>51</sup> leading to persistent neurobiological alterations of the hypothalamic-pituitary-adrenal axis.<sup>4,52,53</sup> Second, socioeconomic adversity in the prenatal and perinatal period is likely to continue during childhood (limiting children's access to social capital, educational resources, and adequate cognitive stimulation) and adulthood, yielding an increased risk for mental disorder, adverse experiences (including trauma), low social support, and suicide risk.<sup>54</sup> Third, inadequate maternal nutrition in pregnancy due to low family resources, or impoverished foetal nutrition of later-born children due to depletion of maternal nutritional reserves during prior pregnancies (thrifty-phenotype hypothesis),<sup>55</sup> may be associated with future mental disorders increasing the suicide risk. Therefore, knowledge of these mechanisms is of utmost importance as they may inform population-based prevention interventions targeting such mechanisms.

This study is based on a systematic literature search with no date limit, and the good quality of the included studies positively affected the quality of the meta-analytic results. Despite these strengths, this study has limitations. First, the large majority of the included studies came from high-income countries, especially from Northern-Europe, with under-representation of low and middle-income countries. This is a fundamental gap that needs to be addressed, as the investigated associations might be different in other socio-economic contexts. Second, our meta-analysis only reported crude associations, therefore the pooled ORs might have overestimated the association between in-utero and perinatal risk factors and suicide risk because of inadequate adjustment for confounding. Third, although most heterogeneity has been explained by differences in age at follow-up across studies, data were not sufficient to conduct

detailed subgroup analyses. Fourth, it was not possible to investigate sex differences. Finally, unpublished studies were not included in our analyses, which might have generated bias.

In conclusion, the available evidence suggests that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, with some differences between suicide-related outcomes (ie, suicide mortality, suicide attempt, and suicidal ideation) that need to be further investigated. These findings emphasize the role of conception and pregnancy as crucial periods for disease prevention from a public health perspective.

## Figures

### Figure 1. Flow chart of study selection

Note: The number of studies included in the quantitative analyses varied by early-life factor and outcome considered.

### Figure 2. Assessed risk factors across the included studies

Note: The figure reports the number of studies in which each individual risk factor was analysed, and includes multiple studies published using the same data.

### Figure 3. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide

Note: The figure shows forest plots reporting the association between in-utero and perinatal risk factors and suicide for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

### Figure 4. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation

Note: The figure shows forest plots reporting the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

### Figure 5. Subgroup analysis by age at follow-up

Note: The figure shows the pooled estimates for each comparison, stratified by age at follow-up.

### Figure 6. Conceptual model of the potential mechanisms linking in-utero and perinatal risk factors and suicide risk

Note: This conceptual model describes possible pathways explaining associations of early-life factors with suicide, as suggested in the reviewed literature. Biological (eg, epigenetic, genetic), environmental (eg, adverse exposure in childhood, low resources) and gene-x-environment mechanisms are suggested.

### **Authors' contribution**

MO, DG, SRD, GT, MCG designed the study; JB elaborate the search strategy and performed the initial search; MO, DB, and MCG performed study selection and quality assessment; MO performed statistical analyses and wrote the first draft of the manuscript; MCG supervised the study; all authors critical reviewed the manuscript and contribute to data interpretation.

### **Conflict of interest statement**

The authors declare no conflict of interest.

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## Research in context

### Evidence before this study

We systematically searched Medline without data and language limitations up to March 6, 2018, using the following keywords: (suicid\* OR “suicide attempt” OR “attempted suicide” OR “suicidal ideation” OR “suicide thoughts” OR “suicidal behavior” OR “suicidal behaviours” OR “completed suicide” OR “suicide risk” OR “suicidality”) AND (“birth order” OR “parity” OR “multiparity” OR “family size” OR “sibship size” OR “number of siblings” OR “birth weight” OR “underweight” OR “maternal age” OR “mother age” OR “paternal age” OR “father age” OR “parent\* age” OR “foetal fetal growth” OR “fetal growth” OR “early life” OR “early-life” OR perinatal OR prenatal) AND (longitudinal OR “population-based” OR cohort OR observational OR prospective OR “registry” OR “register-based”). Most of the retrieved studies investigated risk factors measured during childhood, and a few investigated risk factors during the in-utero and perinatal periods, resulting in 20 relevant studies. No systematic review or meta-analysis was identified. Most studies came from high-quality cohorts and population-based registers. Some studies suggested increased suicide risk for some risk factors (such as increased birth order, low socioeconomic position at birth). However, while similar in quality and design: (i) some studies reported different estimates for the same risk factor; (ii) some studies reported similar estimates (eg, similar Hazard/Odds Ratios) but different confidence intervals, so that only some of the studies could conclude for a statistically significant difference between individuals exposed and non-exposed to the same risk factor; (iii) some studies had different follow-up periods, ie, some extending until adolescence/young adulthood, others extending until adulthood; (iv) almost all studies presented both crude and adjusted estimates, but the choice of the adjustment variables was highly variable across studies; in particular, some studies adjusted for factors occurring between the exposure (eg, low birthweight) and the outcome (eg, suicide), which can bias the estimate of the contribution of the exposure. These differences preclude firm conclusions about the role of these factors on suicide risk.

### Added value of this study

To our knowledge, this is the first systematic review and meta-analysis summarizing the available evidence about the in-utero and perinatal influences on suicide. We found that, across the high-quality included studies, family/parental characteristics at child birth (eg, higher birth order, low mother’s age, single motherhood), low socioeconomic position (eg, low parental education and socioeconomic status), and restricted foetal growth (eg, low birthweight, small for gestational age) were associated with increased suicide risk. No evidence for an association was found for risk factors such as advanced father’s age, low gestational age, obstetric characteristics, and mother’s smoking in pregnancy. Moreover, accounting for the participant’s age at follow-up explained the heterogeneity across studies for most comparisons, without changing the study conclusions.

### Implications of all the available evidence

Evidence suggests that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, with main influences represented by unfavourable family/parental characteristics and restricted foetal growth. However, more studies are necessary to establish the role of those risk factors on suicide attempt and ideation, extend the evidence to understudied influences, and probe their causal role.

Table 1. Characteristics of the included studies

Sample	Study	Study design	Level of analysis	Participants (n)	Year range at birth	Year range at outcome assessment	Follow-up range	Investigated outcomes	Investigated in-utero and perinatal factors
<b>1958 British Birth Cohort</b>									
1958 British Birth Cohort	Geoffroy 2014 <sup>18</sup>	Cohort	Whole population	16 470	1958	1965-2009	7-51	Suicide	Birth order, maternal age, SES, gestational age, birth weight, smoking in pregnancy
1958 British Birth Cohort	Geoffroy 2018 <sup>29</sup>	Cohort	Whole population	8 905	1958	2003	45-45	Ideation	Birth order, maternal age, SES, birth weight
<b>ALSPAC</b>									
	Easey 2019 <sup>56</sup>	Cohort	Whole population	2571	1991-1992	up to 2008	up to 16	Attempt	Birth order
	Page 2014 <sup>32</sup>	Cohort	Whole population	1 806	1991-1992	2007-2009	16-18	Attempt	SES, maternal education
<b>Born in Washington State, US, in 1968–96</b>	Li 2003 <sup>57</sup>	Register	Whole population	23 882	1968-1996	NA	1-19	Suicide	Birthweight
<b>CHDS</b>									
CDHS	Fergusson 1999 <sup>58</sup>	Cohort	Whole population	1 025	1977-1998	1992-1996	up to 18	Attempt	Maternal age
CDHS	Fergusson 2000 <sup>31</sup>	Cohort	Whole population	1 265	1977-1998	1992-1998	up to 21	Attempt, ideation	Maternal age, single mother, SES, maternal education
<b>Copenhagen Perinatal Cohort 1959-1961</b>	Sorensen 2009 <sup>59</sup>	Register	Whole population	7 177	1959-1961	1969-2005	10-46	Suicide	SES
<b>Danish born in 1966–1996</b>									
Danish born in 1966	Christofferssen 2003 <sup>60</sup>	Register	Whole population	84 765	1966	1981-1993	14-27	Attempt	Maternal age
Danish born in 1966–1996	Mok 2017 <sup>61</sup>	Register	Whole population	1 793 681	1966-1996	1981-2006	15-40	Suicide	Maternal age, paternal age
<b>Danish Metropolit Cohort</b>	Osler 2008 <sup>19</sup>	Cohort	Whole population	9 359	1953	1972-2002	19-49	Suicide, attempt	Single mother, SES, birthweight
<b>E3N Cohort 1990</b>	Verdoux 2007 <sup>36</sup>	Cohort	Sibling design	3 127	NA	up to 2004	NA	Suicide	Exposure to diethylstilboestrol
<b>Finnish born in 1922-1989</b>									
Finnish born in 1922-1987	Saarela 2016 <sup>62</sup>	Register	Sibling design	254 059	1922-1987	1987-2011	0-89	Suicide	Birth order
Finnish born in 1987-1989	Ekblad 2010 <sup>34</sup>	Register	Whole population	179 869	1987-1989	1987-2007	0-20	Suicide	Smoking in pregnancy
<b>Helsinki Birth Cohort Study 1934–1944</b>									
Helsinki Birth Cohort Study 1934–1944	Lahti 2014 <sup>63</sup>	Register	Whole population	13 242	1934-1944	1969-2010	24-76	Suicide, attempt	Birth order
Helsinki Birth Cohort Study 1934–1944	Lahti 2015 <sup>64</sup>	Register	Whole population	12 597	1934-1944	1969-2010	25-76	Suicide, attempt	Gestational age, SGA
<b>Johns Hopkins Collaborative Perinatal Study</b>	Nomura 2007 <sup>33</sup>	Cohort	Whole population	1 525	1960-1964	1992-1994	27-33	Ideation	Gestational age, birthweight, head circumference, APGAR
<b>National Longitudinal Survey of Children and Youth</b>	Dykxhoorn 2017 <sup>65</sup>	Cohort	Whole population	6 388	1994-2009	NA	12-25	Ideation	Maternal age, prenatal care after 20 weeks of gestation
<b>Northern Finland Birth Cohort 1966</b>									
Northern Finland Birth Cohort 1966	Alaräisänen 2012 <sup>38</sup>	Cohort	Whole population	10 742	1966	1967-2005	up to 39	Suicide, attempt	Birth order, maternal age, single mother, SES, antenatal depression, unwanted pregnancy

Northern Finland Birth Cohort 1966	Miller 2010 <sup>66</sup>	Cohort	Whole population	10 965	1966	1967-2005	up to 39	Suicide	Maternal age, SES, paternal age
Northern Finland Birth Cohort 1966	Sauvola 2001 <sup>67</sup>	Cohort	Whole population	11 017	1966	1982-1994	16-28	Suicide	Single mother
<b>Norwegians born in 1967–1997</b>									
Norwegians born in 1967–1996	Bjørngaard 2013 <sup>26</sup>	Register	Whole population and sibling design	1 690 306	1967-1996	1979-2008	12-41	Suicide	Birth order, maternal age, single mother, maternal education, paternal education, interbirth spacing
Norwegians born in 1967–1976	Gravseth 2010 <sup>68</sup>	Register	Whole population	610 359	1967-1976	1986-2004	10-37	Suicide	Birth order, single mother
Norwegians born in 1967–1997	Risnes 2016 <sup>69</sup>	Register	Whole population and sibling design	1 562 647	1967-1997	1981-2011	15-45	Suicide	Gestational age
<b>Pelotas Birth Cohort</b>	Barros 2018 <sup>70</sup>	Cohort	Whole population	3 528	1982	2012	30	Attempt	SES
<b>Scottish born in 1969-1988</b>									
Scottish born in 1969-1986	Riordan 2006 <sup>71</sup>	Register	Whole population	1 061 830	1969-1986	1981-2003	12-34	Suicide	Birth order, maternal age, SES, gestational age, birthweight
Scottish born in 1969-1986	Riordan 2012 <sup>45</sup>	Register	Whole population	897 685	1975-1988	1987-2007	12-32	Suicide	Birth order, maternal age, SES, gestational age, birthweight, family size
<b>Scottish longitudinal survey of young people</b>	Young 2011 <sup>72</sup>	Cohort	Whole population	2 157	1984	1999	up to 15	Attempt	Birth order, maternal age, birthweight, number of birth complications,
<b>Swedish born in 1932-1997</b>									
Swedish born in 1973-1997	Class 2014 (a) <sup>43</sup>	Register	Whole population and sibling design	2 308 032	1973-1997	2009	12-36	Attempt	Birthweight
Swedish born in 1973-1997	Class 2014 (b) <sup>37</sup>	Register	Whole population	2 197 707	1973-1997	1985-2009	12-36	Suicide, attempt	Prenatal stress
Swedish born in 1983-1996	Cnattingius 2011 <sup>17</sup>	Register	Whole population and sibling design	1 449 333	1983-1996	1993-2007	10-24	Suicide	Birth order, maternal age, single mother, gestational age, birth length, birthweight, paternal age, smoking in pregnancy, maternal education, SGA, number of birth complications, head circumference, hypertensive disease, placenta abruption, mode of delivery
Swedish born in 1973-1997	D'Onofrio 2013 <sup>73</sup>	Register	Whole population and sibling design	3 300 708	1973-1997	1985- 2009	12-37	Attempt	Gestational age
Swedish born in 1973-1997	D'Onofrio 2014 <sup>30</sup>	Register	Whole population and sibling design	2 293 032	1973-1997	1985- 2009	12-37	Attempt	Paternal age
Swedish born in 1973-1979	Ekéus 2006 <sup>74</sup>	Register	Whole population	292 129	1973-1979	1990-2002	17-29	Suicide, attempt	Maternal age
Swedish born in 1973-1980	Mittendorfen-Rutz 2004 <sup>16</sup>	Register	Whole population	713 370	1973-1980	1983-1999	10-26	Suicide, attempt	Birth order, maternal age, birthweight, birth length, hypertensive disease, mode of delivery

Swedish born in 1973-1980	Mittendorfen-Rutz 2008 <sup>75</sup>	Register	Whole population	318 953	1973-1980	1991-1999	18/19-26	Attempt	Gestational age, birthweight, birth length
Swedish born in 1973-1983	Niederkrotenthaler 2012 <sup>76</sup>	Register	Case-control	14 976	1973-1983	1983-2004	10-31	Suicide, attempt	Birth order, maternal age, gestational age, birthweight, paternal age, SGA, birth length
Swedish born in 1932-1980	Rostila 2014 <sup>27</sup>	Register	Sibling design	102 824	1932-1980	1981-2002	up to 70	Suicide	Birth order, maternal age
Swedish born in 1946-1968	Von Borczyskowski 2010 <sup>77</sup>	Register	Whole population	2 936 224	1946-1968	1987-2001	19-55	Suicide	Maternal age, SES, paternal age
<b>Swiss National Cohort</b>	Steck 2018 <sup>78</sup>	Register	Whole population	2 395 677	1990-2000	2000-2008	10-18	Suicide	Birth order, maternal age, single mother, SES, paternal age, parental education
<b>Taiwanese born in 1978-1993</b>	Chen 2013 <sup>28</sup>	Register	Case-control	123 504	1978-1993	1993-2008	15-30	Suicide	Birth order, maternal age, single mother, maternal education, paternal education
<b>Uppsala University Hospital in 1915-1929</b>	Danziger 2011 <sup>79</sup>	Register	Whole population	11 650	1915-1929	1960-2002	31-87	Suicide	Birth order, maternal education, single mother, SES, gestational age, birth weight, SGA

ALSPAC, Avon Longitudinal Study of Parents and Children; CHDS, Christchurch Health and Development Study; NA, not available; SGA, Small for gestational age; SES, Socioeconomic status

Table 2. Quality assessment according to the Newcastle-Ottawa Scale criteria

Sample	Study and year	Selection				Comparability	Outcome			Qualit y score (0-9)
		Representa tiv eness (0-1)	Selection non exposed (0- 1)	Ascertainm ent exposure (0-1)	Outcome not present at study start (0- 1)	Case/control comparability (0- 2)	Assesse ment of outcome (0-1)	Length of follow-up (0-1)	Adequacy of follow- up (0-1)	
1958 British Birth Cohort										
1958 British Birth Cohort	Geoffroy 2014 <sup>18</sup>	1	1	0	1	2	1	1	1	8
1958 British Birth Cohort	Geoffroy 2018 <sup>29</sup>	1	1	0	1	2	1	0	0	5
ALSPAC										
ALSPAC	Easey 2019	1	1	1	1	2	0	1	1	8
ALSPAC	Page 2014 <sup>32</sup>	1	1	1	1	2	0	1	1	8
Born in Washington State, US, in 1968–96										
CHDC	Li 2003 <sup>57</sup>	1	1	1	1	1	1	1	1	8
CHDC										
CHDC	Fergusson 1999 <sup>58</sup>	1	1	0	1	1	0	1	1	6
CHDC	Fergusson 2000 <sup>31</sup>	1	1	0	1	2	0	1	1	7
Copenhagen Perinatal Cohort 1959-1961										
Danish born in 1966–1996	Sorensen 2009 <sup>59</sup>	1	1	1	1	1	1	1	1	8
Danish born in 1966–1996										
Danish born in 1966	Christofferssen 2003 <sup>60</sup>	1	1	1	1	2	1	1	1	9
Danish born in 1966–1996	Mok 2017 <sup>61</sup>	1	1	1	1	2	1	1	1	9
Danish Metropolit Cohort										
E3N Cohort 1990	Osler 2008 <sup>19</sup>	1	1	1	1	0	1	1	0	6
Finnish born in 1922-1989	Verdoux 2007 <sup>36</sup>	1	1	0	1	1	0	1	1	6
Finnish born in 1922-1989										
Finnish born in 1922-1987	Saarela 2016 <sup>62</sup>	1	1	1	1	2	1	1	1	9
Finnish born in 1987-1989	Ekblad 2010 <sup>34</sup>	1	1	1	1	2	1	1	1	9
Helsinki Birth Cohort Study 1934–1944										
Helsinki Birth Cohort Study 1934–1944	Lahti 2014 <sup>63</sup>	1	1	1	1	2	1	1	1	9
Helsinki Birth Cohort Study 1934–1944	Lahti 2015 <sup>64</sup>	1	1	1	1	2	1	1	1	9
Johns Hopkins Collaborative Perinatal Study										
NLSCY	Nomura 2007 <sup>33</sup>	1	1	1	1	2	0	1	1	8
Northern Finland Birth Cohort 1966	Dykxhoorn 2017 <sup>65</sup>	1	1	0	1	NA	0	1	0	4
Norwegian born in 1967–1996										
Norwegian born in 1967–1976	Bjørngaard 2013 <sup>26</sup>	1	1	1	1	2	1	1	1	9
Norwegian born in 1967–1997	Gravseth 2010 <sup>68</sup>	1	1	1	1	1	1	1	1	8
Pelotas Birth Cohort	Risnes 2016 <sup>69</sup>	1	1	1	1	2	1	1	1	9
Scottish born in 1969-1988	Barros 2018	1	1	0	1	0	0	1	1	5



Scottish born in 1969-1986	Riordan 2006 <sup>71</sup>	1	1	1	1	2	1	1	1	9
Scottish born in 1969-1986	Riordan 2012 <sup>45</sup>	1	1	1	1	2	1	1	1	9
<b>Scottish longitudinal survey of young people</b>	Young 2011 <sup>72</sup>	1	1	0	1	2	0	1	1	7
<b>Swedish born in 1932-1997</b>										
Swedish born in 1973-1997	Class 2014 (a) <sup>43</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	Class 2014 (b) <sup>37</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1983-1996	Cnattingius 2011 <sup>17</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	D'Onofrio 2013 <sup>73</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	D'Onofrio 2014 <sup>30</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1979	Ekéus 2006 <sup>74</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1980	Mittendorfen-Rutz 2004 <sup>16</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1980	Mittendorfen-Rutz 2008 <sup>75</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1983	Niederkrotenthaler 2012 <sup>76</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1932-1980	Rostila 2014 <sup>27</sup>	1	1	1	1	2	1	1	1	9
Swedish born in 1946-1968	Von Borczyskowski 2010 <sup>77</sup>	1	1	1	1	2	1	1	1	9
<b>Swiss National Cohort</b>	Steck 2018 <sup>78</sup>	1	1	1	1	2	1	1	1	9
<b>Taiwanese born in 1978-1993</b>	Chen 2013 <sup>28</sup>	1	1	1	1	2	1	1	1	9
<b>Uppsala University Hospital in 1915-1929</b>	Danziger 2011 <sup>79</sup>	1	1	1	1	2	1	1	1	9

ALSPAC, Avon Longitudinal Study of Parents and Children; CHDS, Christchurch Health and Development Study; NA, not applicable